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August 31, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

RE: Draft Guidance for Industry of Establishing Pregnancy Registries
Docket Number 99D- 154 1

Abbott Laboratories participates in two pregnancy registries: an Antiepileptic Drug Registry and an Antiretroviral Pregnancy Registry. We agree with the FDA's assessment of the usefulness of pregnancy registries in various clinical circumstances and agree with the need for agency guidance in formulating studies in order to increase registry effectiveness and decrease variability of interpretation and reporting.

We present the following comments in response to the agency's "Guidance For Industry" regarding "Establishing Pregnancy Registries":

When Is A Pregnancy Registry Needed?

The guidance suggests that any product expected to be used commonly by women of reproductive potential (i.e. especially new molecular entities) would be considered to be appropriate for pregnancy registries. Furthermore, is suggested that "ideally, a pregnancy registry should be established as early as possible after new product is deemed approvable". As the guidelines point out, 60 percent of pregnancies are unplanned. Since many of these patients are receiving drug therapy, the number of registries and associated costs might be prohibitive. Accordingly, it seems prudent to narrow the recommendations for registries to situations where there is a suspicion of teratogenicity associated with that the specific drug or drug group. Elsewhere in the guidance it is suggested that there is "potential need for registries of older products or comparative registries of old and new products". We suggest clarification of these broad recommendations.

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Regulatory Reporting:
There is a discrepancy in what the guidance is expecting should be reported to the FDA. First, the guidance states that sponsors are required to report spontaneous reports of serious adverse outcomes to the FDA when identified during the recruitment process, even if not included in the analysis, and that reports should be identified as having been reported to the registry. Later, the guidance states that pregnancy registries should be considered as PMS studies (citing 8/97 Guidance for Industry), reporting only serious events where there is a causality that the event may be related to the product. Then, the Pregnancy Registry Guidance later recommends that registries requested by sponsors be: subject to 1.5day reporting in addition to periodic reporting of nonserious and serious, labeled events, suggesting that all events be reported. The guidance needs to clearly define what type of reports the FDA expects to receive when a pregnancy registry program is in place.

The Registry Guidance also states that interim and annual reports be submitted by the registry, to the NDA or PLA. The time frame for interim reports and periodic dates for annual reports needs to be detailed. Also, it needs to be clarified whether these reports are different from the annual/periodic reports expected of the sponsors, and understood that this will be a form of duplicate reporting.

Periodic/regulatory reporting should be handled as a separate section. Differentiation between what reports are expected from sponsor companies vs what reports are expected from the Registries themselves, would be a helpful addition.

Clarification of the appropriate mechanism for reporting is necessary in order to decrease reporting variability between companies and between registries. Variability may introduce reporting bias into the data received by the agency and therefore make interpretation of the data even more difficult. The institution of a consistent guideline for reporting should negate the necessity for waivers.

Study Outcomes:
The guidelines suggest that “a minimal list of outcomes that should be collected includes maternal adverse event, labor and delivery complications, and major categories of pregnancy outcomes including spontaneous abortion, elective termination, fetal deaths/stillbirth and live born infants.” The nature of the registry and goals of any registry need to be promulgated in the original protocol; these goals should determine what data are needed for final analysis. Birth defects registries, by definition, would not require the collection of maternal adverse events or labor/delivery complications. Inclusion of this wide spectrum of events into any single registry would likely introduce the need to contact multiple sources in order to complete data collection and, therefore, make the cost and low likelihood of adequate data collection prohibitive.

Enrollment:
The experience to date suggest that even with diligent recruiting, enrollment of sufficient cases for adequate analysis is difficult. Currently, DDMAC regulations contain requirements for distribution of package inserts in addition to descriptions of the registries themselves. This makes efficient and effective notification of potential enrollees of patients problematic.

Additionally, in some instances the registry handles multiple drugs (ie all antiretroviral) which further complicates issue of package insert distribution. Furthermore, DDMAC currently provides for review of materials for products where the indication for use is approved. Guidelines which address unlabeled use would be helpful.

Respectfully,

Charles F. Schwamlein, MD, MPH
Director/Epidemiology

cc: Frank Pokrop
Rose E. Cunningham

A6/CFS/pregreg/kat

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